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REVIEW ARTICLE

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The technique of ophthalmic arterial infusion therapy for patients with intraocular retinoblastoma

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Abstract Recently, there has been increasing interest in treating intraocular retinoblastoma with systemic chemotherapy combined with focal laser therapy and cryotherapy instead of radiotherapy. We developed a system of selective ophthalmic arterial infusion (SOAI) therapy, administering melphalan, the agent which had the greatest effect on retinoblastoma in a clonogenic assay. The SOAI system consists of a combination of a micro-balloon, a guiding catheter, and a flushing hub. After selective catheterization to the cervical segment of the internal carotid artery by the guiding catheter, the micro-balloon was propelled to the portion just distal to the orifice of the ophthalmic artery. During temporary occlusion of the internal carotid artery, melphalan was infused from the introduced catheter tip. We treated 187 patients with intraocular retinoblastoma with SOAI; 563 SOAIs were performed for 610 eyes. The technical success rate was 97.51%. Fourteen examinations failed. No significant complication due to catheterization (including brain infarction) was detected. SOAI, using the balloon occlusion technique, is safe, and its use will prevent the side effects that occur with systemic chemotherapy, and eliminate the need for irradiation and enucleation.

Key words Retinoblastoma · Chemotherapy · Arterial infusion · Ophthalmic artery

Introduction

Simultaneous external beam radiotherapy has been shown to be an effective treatment for retinoblastomas.[1,2] The recurrence rate in radiotherapy is approximately 40%, and there is a 90% risk of cosmetic deformity, cataracts, and radiation retinopathy. Moreover, radiotherapy further increased the risk of mortality from a second neoplasm.[3] Therefore, there is increasing interest in treating intraocular retinoblastoma with chemotherapy combined with focal laser therapy and cryotherapy[4,5] (Fig. 1).

Inomata and Kaneko[6] showed, in a clonogenic assay, that melphalan, compared with other commonly used agents had the greatest effect on retinoblastoma, and the sensitivity was enhanced at 42°C.

To reduce the side effects of melphalan and to obtain a better response, we developed a system of selective ophthalmic arterial infusion (SOAI), with the goal of preserving the eye.[7]

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Subjects, materials, and methods

Study group

Between January 1988 and January 2001, a total of 187 patients (103 boys and 84 girls) with intraocular retinoblastoma were treated with SOAI at the National Cancer Center Hospital, Japan. The age of the retinoblastoma patients ranged from 1 month and 5 days to 11.5 years (mean, 2.47 years). One hundred patients had bilateral and 87 patients had unilateral retinoblastoma; 563 SOAIs were performed (Fig. 2) for 610 eyes (mean, 3.01 SOAIs/patient; range, 1–12 SOAIs/patient). In 73.59% of the 549 successful SOAIs we combined the SOAI, with thermotherapy, by microwave and/or laser (Table 1). All SOAI were done under general anesthesia.

Micro-balloon catheters

Single-lumen specially designed silicone balloons (Kaneka Medix, Osaka, Japan) were used: small, 4.0 mm; large, 5.0 mm, depending on the fully inflated diameter (Fig. 3). The outside diameters of the catheter tubing were 0.6 mm

and 0.7 mm. Because these balloon catheters are being redesigned, the device can no longer be purchased.

Guiding catheters

We used 4-Fr polyethylene simple curved catheters (Cathex, Tokyo, Japan).

Technique

The sheath for the 4-Fr catheter was introduced, using the Seldinger technique. The Y adapter (flushing hub) was attached to the proximal end of the 4-Fr introducer catheter, and the deflated balloon catheter filled with contrast medium was passed through the introducer catheter (Fig. 4).

Under fluoroscopic control, selective catheterization to the cervical segment (C1) (Fig. 5[8,9]) of the internal carotid artery (ICA) is done with the introducer catheter within the micro-balloon, without using a guidewire. Partial inflation

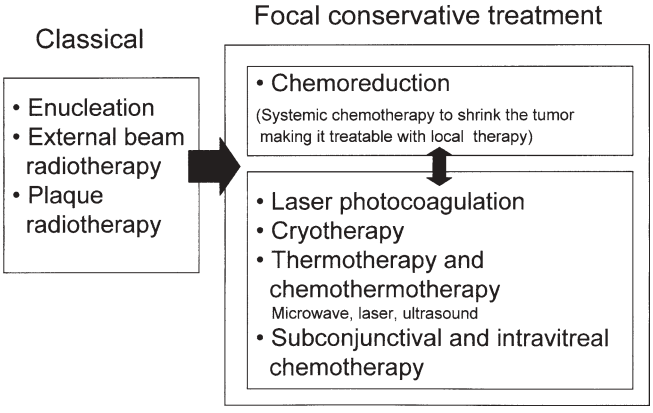


Fig. 1. Management of retinoblastoma

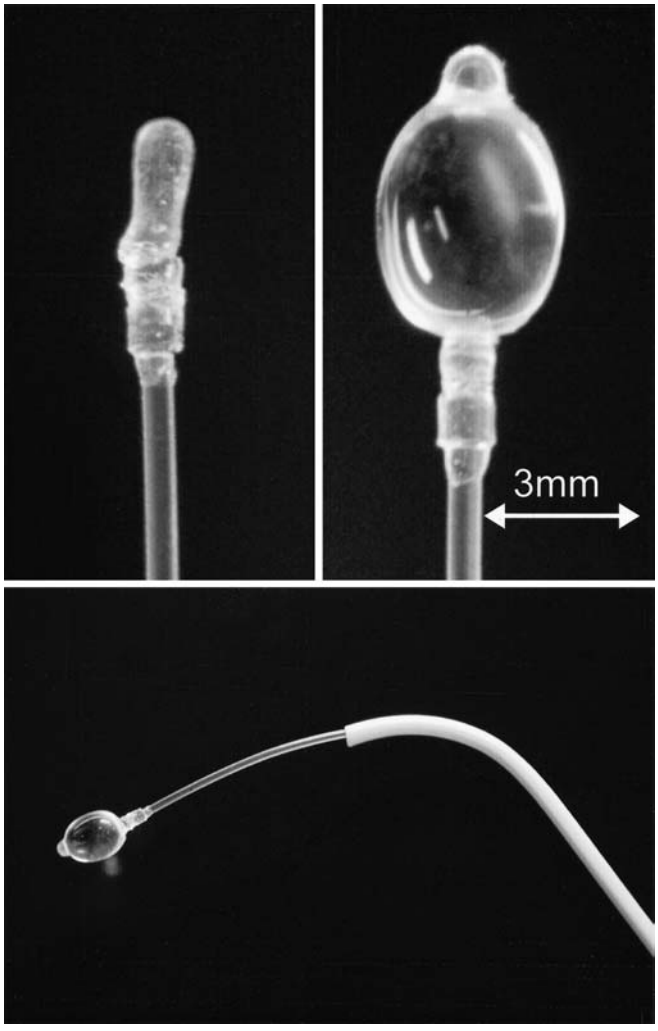
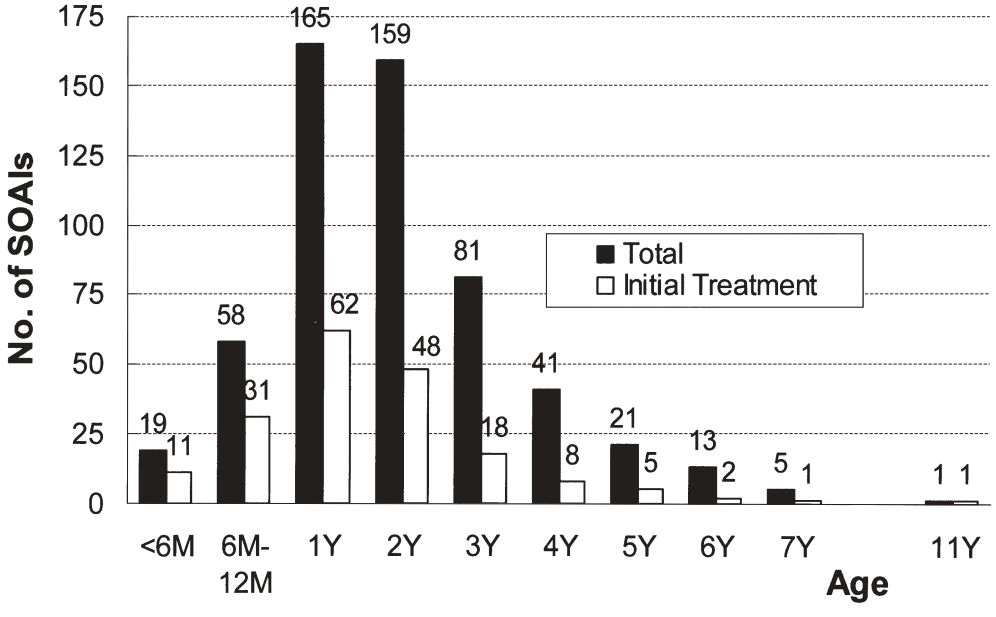


Fig. 3. Micro-balloon (large)

Fig. 2. Number of selective ophthalmic arterial infusions (*SOAIs*) classified by age. *Y*, years; *M*, months



of the balloon and a test injection with contrast medium through the side arm of the Y adapter (Fig. 4, *A*) may help this catheterization and avoid intimal injury. After the tip of the introducer catheter reaches C1, the balloon catheter is inflated to near the caliber of the C2–4 segments. To advance the balloon tip, we use the following maneuvers:

1. Simple manual advancement. The properly inflated balloon catheter is propelled by blood flow and simple manual advancement of the distal tubing of the balloon.
2. A 1-ml flush. A powerful flush with a 1-ml syringe through the arm of the Y adapter propels the balloon tip distally and the balloon tubing through the introducer catheter.
3. Repetition of inflation and deflation of the balloon tip.

The balloon can easily be advanced to the proximal portion of the largest curve of the carotid siphon (around the border between C4-C5) by using maneuvers (1) and (2) only.

If the balloon tip is not propelled beyond the carotid siphon by the repetition of maneuvers (1) and (2), maneuver (3) should be tried. As the diameter of the balloon is changed, the direction of the balloon tip and the degree of force received from the blood flow will be changed. At the point that the the balloon tip receives adequate force against the friction, it will move beyond the orifice of the ophthalmic artery (Fig. 6).

During temporary occlusion at the portion just distal to the orifice of the ophthalmic artery, a spot angiogram (Fig. 7) was taken, and melphalan (5–40 $mg \cdot m^{2-1}$) was infused from the introducer catheter. A high dose ($\geq$20 $mg \cdot m^{2-1}$) of melphalan was administered to only 12 patients (20 SOAIs) in the early period of this therapy (Fig. 8).

Results

The technical success rate was 97.51%. Fourteen examinations (11 patients, mean age, 3.33 years) failed; Table 2 shows the causes of technical failure. There was no significant complication (including brain infarction) due to catheterization. Bradycardia occurred within a few seconds of arterial injection. Facial redness and mild swelling around the eyelid were also observed frequently.

Table 1. Combinations of SOAI and thermotherapy

SOAI only	145 (26.4%)
SOAI with microwave thermotherapy	256 (46.6%)
SOAI with laser thermotherapy	132 (24.1%)
SOAI with microwave and laser thermotherapy	16 (2.9%)
Total	549

SOAI, selective opthalmic arterial infusion

Table 2. Technical failures

Non-visualization or narrowing of OpA	5
Arterial puncture failure because of obesity	2
Anomaly (OpA arising from ECA)	2
Drop in blood pressure	2
Spasm of ICA	1
Severe tortuousness of ICA (C2)	1
Total	14 (11 patients)

OpA, ophthalmic artery; ECA, external carotid artery; ICA, internal carotid artery; C2, petrons segment

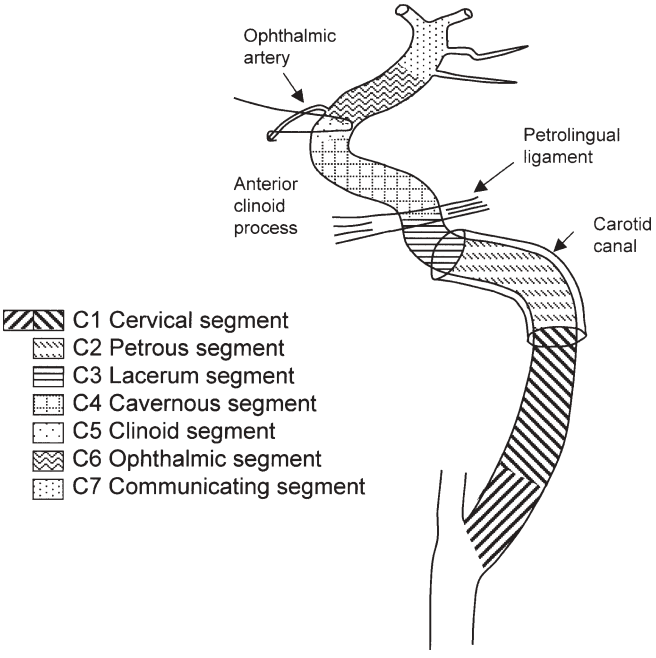


Fig. 5. Segmental anatomy of the internal carotid artery

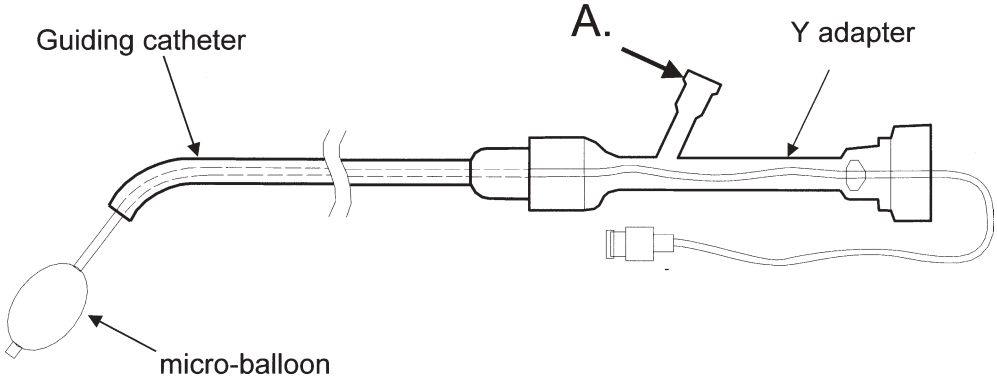


Fig. 4. The SOAI system. *A*, side arm of the Y adapter

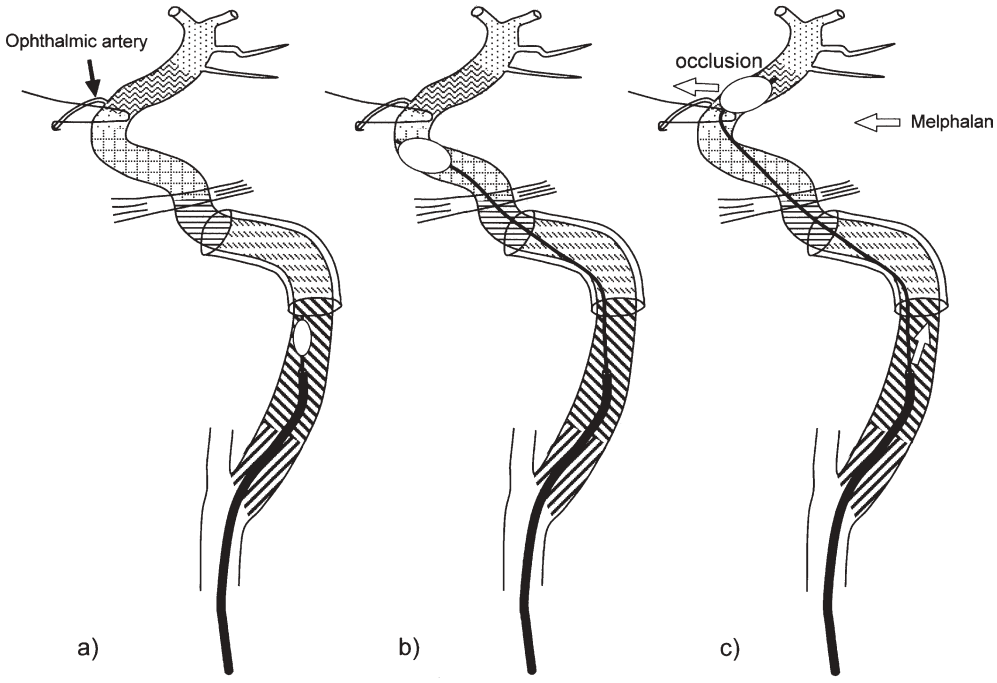


Fig. 6a–c. Schema of arterial infusion to ophthalmic artery

Fig. 7. Selective left carotid angiogram of 2-year-old patient. The balloon tip (*arrow*) was placed in the ophthalmic segment distal to the orifice of the ophthalmic artery. *Arrow head*, ophthalmic artery

Discussion

For adults, superselective catheterization directly to the ophthalmic artery is usually done by using a microcatheter; the procedure is relatively safe and there is no technical difficulty. In cases of central retinal vein occlusion, superselective intraophthalmic artery fibrinolytic therapy is performed by using 1.8-Fr or 1.5-Fr microcatheters. We have several experiences of using superselective ophthalmic arterial infusion therapy for adult patients with intraocular melanoma. However, in an infant or child, it is difficult to insert a microcatheter in the ophthalmic artery because of the artery's small diameter. If the ophthalmic artery of the child can be superselectively catheterized, there is a higher risk of intimal injury than in adults. Therefore, we selected

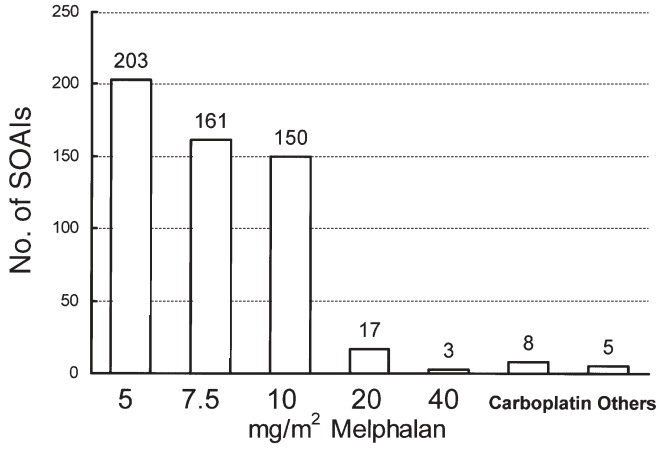


Fig. 8. Dose of melphalan

a method without using superselective catheterization to the ophthalmic artery, and developed the technique using a micro-balloon. We occluded the ICA just distal to the orifice of the ophthalmic artery by using a micro-balloon, and infused the drug from a guide catheter. In this procedure, most of the drug would flow into the ophthalmic artery, and there is no risk of intimal injury to the ophthalmic artery.

Several small but important branches arise from the ICA proximal to the origin of the ophthalmic artery. In our method, the drug could flow into these branches, such as the caroticotympanic artery, the meningohypophyseal artery, the artery of the inferior cavernous sinus, the capsular arteries of McConnell, and the superior hypophyseal arteries. Therefore, strictly speaking, our infusion method is not truly selective. If the guide catheter is catheterized into near the orifice of the ophthalmic artery, the drug may not flow into the other branches, but there may be an increase in the risk of injury to the ICA, because we do not use a guide wire to advance the guide catheter in this system.

Moreover, vascular anomalies may prevent us from performing ophthalmic infusion. Persistent trigeminal artery (PTA), the most common of the carotid-basilar anastomoses, arises from the cavernous segment of the ICA. If a PTA exists, most of the drug would flow into the PTA and the basilar artery.

When melphalan was administered, bradycardia always occurred. The duration of bradycardia was a few seconds, and there was no experience of persistent bradycardia. The same phenomenon occurred with the administration of contrast medium. We suppose that the bradycardia was a vasovagal reflex caused by the drug flow into the ophthalmic artery. From a different point of view, when bradycardia occurred, we thought that the drug had been successfully administered into the ophthalmic artery.

In cases of severe tortuosity of the carotid siphon preventing the advancing of the micro-balloon, we used the foregoing maneuvers. Recently, the GuardWire (Medtronic, Santa Rosa, CA, USA) was developed; this is a dedicated guidewire that has a distal-balloon protection system for vascular intervention.[10,11] This occlusion balloon device may easily be advanced to the distal portion of the ICA, but it has a stiffer shaft than the micro-balloon we use. Although we have no experience of using the GuardWire for ophthalmic infusion, we suppose that it may injure the intima of the carotid siphon because of its stiff shaft.

There are many difficulties in analysis of the efficacy of SOAI. Many SOAIs were combined with laser and/or microwave thermotherapy. In recent years, for the patients who had vitreous seeding, intravitreal injection of melphalan was combined with SOAI. Some patients had external beam or plaque radiotherapy before or between performances of SOAI, and in some patients, enucleation of one eye had been performed before SOAI. To compare the efficacies of SOAI and systemic chemotherapy, a control study would be necessary, but it is difficult to perform a control study in our circumstances. Our urgent problem is to establish a way to analyze the efficacy of SOAI combined with thermotherapy for patients with various treatment histories. In the present situation, the eye preservation rate is the only standard for theraputic efficacy.

Conclusion

For patients with intraocular retinoblastoma, SOAI, using a balloon occlusion technique combined with thermotherapy, is safe, and its use will prevent the side effects that occur with systemic chemotherapy, and eliminate the need for irradiation and enucleation.

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